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A Vaccine for Alzheimer's Disease?®

By J. Travis

Stunning, unexpected results from experiments with mice have given scientists cautious optimism that simple injections can prevent or slow the development of Alzheimer's disease. Such therapy might even reverse some of the brain damage in people already afflicted with the devastating disorder.

Scientists at Elan Pharmaceuticals in South San Francisco, Calif., injected mice with beta-amyloid, the very protein fragment suspected of causing Alzheimer's disease. This immunization, they found, generated antibodies that prevented the accumulation of beta-amyloid within the mouse brain and even cleared existing amyloid deposits, known as plaques.

"This is the first time that anyone has stopped the development of amyloid plaques in a mouse model of Alzheimer's," says Marcelle Morrison-Bogorad of the National Institute on Aging in Bethesda, Md. "This is a major step forward. Conceivably, you could immunize people against Alzheimer's disease."

"It's wild and amazing," agrees Sangram S. Sisodia of the University of Chicago.

Several years ago, Elan's Dale Schenk wondered whether the immune system could be aroused to clear the amyloid deposits seen in the brains of people with Alzheimer's. To test Schenk's idea, Elan scientists turned to genetically engineered mice that develop large numbers of plaques because they harbor a mutant version of the human gene for the protein that forms beta-amyloid. The researchers began injecting these mutant mice with human beta-amyloid and an immune-stimulating agent called an adjuvant.

Starting at 6 weeks of age, the mice received the injections once a month for nearly a year. At the end of the immunization, the scientists examined the rodents' brains and found that seven out of nine had virtually no amyloid deposits. Both of the two remaining mice had significantly less beta-amyloid than untreated animals, Schenk's team reports in the July 8 *Nature*. The treated mice also lacked other brain alterations associated with amyloid deposits, such as misshapen nerve connections.

Taken aback by their findings, the investigators then gave a similar series of injections to 11-month-old mice that had already developed amyloid plaques. The shots prevented additional amyloid deposits and even triggered clearance of some existing plaques, the scientists found.

The immunizations create large amounts of antibodies that bind to beta-amyloid, prompting Schenk to speculate that some of the antibodies circulating in the blood sneak into the brain and latch onto any plaques. That may alert the brain's immune cells, microglia and monocytes, to clear the beta-amyloid.

"It's as if the microglia and monocytes are garbagemen and the antibodies act as signposts stuck on the garbage," says Schenk. He notes that Elan has found beta-amyloid inside those immune cells in the brains of treated mice.

The immunization strategy may resolve the great debate in Alzheimer's disease research. Most

Exhibit G

neuroscientists believe that the accumulation of beta-amyloid within the brain somehow causes the cell death and resulting memory impairment seen in people with the illness. Other investigators suggest accumulations of a protein called tau are the real villains in Alzheimer's disease.

If the beta-amyloid shots prevent plaques in people as well as mice, "we're going to test the amyloid hypothesis very thoroughly," says Schenk.

While the benefits of a vaccine for Alzheimer's are obvious, it's less clear whether the immunization strategy will serve people already impaired. "Even if you get rid of the amyloid deposits, what will happen to the patients? Will they level off or actually get better?" asks Sisodia. Eliminating amyloid deposits may not prevent accumulation of the tau protein, he notes.

Still, Sisodia marvels at Elan's novel strategy. Almost all scientists would have dismissed the immunization approach, he notes, because of the "dogma" that the so-called blood-brain barrier keeps circulating antibodies out of the brain.

The immunization tactic may also prove useful for the other diseases in which amyloids accumulate in the brain or elsewhere, notes Peter H. St. George-Hyslop of the University of Toronto. The approach might even tackle Huntington's and Parkinson's diseases, both of which involve abnormal brain aggregations of other proteins, he speculates.

While the mice given the beta-amyloid injections suffered no obvious ill effects, scientists caution that the shots could trigger an autoimmune response to the beta-amyloid precursor protein, which is present throughout the body.

By the end of the year, Schenk and his colleagues plan to begin testing the immunization approach on people with mild to moderate Alzheimer's disease. Their initial goal is to confirm the strategy's safety, but they'll also monitor the people for cognitive improvement or slower-than-normal decline. Elan would then like to quickly launch a prevention trial in people known to have a high risk of developing Alzheimer's disease.

"If it does work, it would stand as one of the great scientific success stories of all time," says Morrison-Bogorad.

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